(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/057229 A1

(51) International Patent Classification[7]: C07D 207/34, A61K 31/40

(21) International Application Number: PCT/IN01/00006

(22) International Filing Date: 19 January 2001 (19.01.2001)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/057229 A1

(54) Title: FORM V CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-ß,$G(D)-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1- HEPTANOIC ACID HEMI CALCIUM SALT. (ATORVASTATIN)

(57) Abstract: A novel crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1- heptanoic acid hemi calcium salt designated as Form V is characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation which is useful as an agent for treating hyperlipidemia and hypercholesterolemia.

Form V crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt. (ATORVASTATIN)

FIELD OF THE INVENTION

The present invention relates to a process for the production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (ATORVASTATIN). The present invention further relates to a method of production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt and its isolation. This novel crystalline form of atorvastatin is useful as a pharmaceutical agent, as an inhibitor of the enzyme 3-hydroxy-3 methylglutaryl-coenzyme.A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

BACKGROUND OF THE INVENTION

Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain intermediates used in the synthesis of atorvastatin. United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the

ring-opened acid of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2:1). The process by which atorvastatin is produced should be

(i) easily scaled up for commercial production

(ii) The product should be in a form that is readily filterable and easily dried.

(iii) The product is stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

To overcome the above disadvantages, the present invention provides atorvastatin in a new crystalline form designated Form V. Form V atorvastatin has different physical characteristics compared to the previous crystalline or amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ, d-spacings, and relative intensities measured on a STOE/STADI-P X-ray powder diffractometer with germanium monochromated Cu K alpha 1(L =1.54056 Angstroms) Siemens D-500 diffractometer with CuK. Radiation:

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9
8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5

26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7
30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

Further, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker DRX-500MHz spectrometer:

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5 122.7

	120.1 117.0 112.9
C8, C10	72.3 69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

The present invention further relates to a process for the preparation of Form V atorvastatin Calcium and hydrates thereof which comprises

(i) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;

(ii) filtering to get the solid;

(iii) drying to get Form V atorvastatin calcium.

The ratio of water and absolute alcohol is in the range of 3 :1 to 8:1, preferably 4.67 : 1.

Stirring is carried at 25 - 50 deg centigrade, preferably 40 deg centigrade.

The stirring is carried for 10 - 25 hrs, preferably 17 hours.

The final product is dried in vacuum tray drier.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying Figures 1 to 4, short particulars of which are given below.

Figure 1:

Diffractogram of heterogeneous mixture of atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure

Diffractogram of Form V atorvastatin. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 3:

The solid state ^{13}C nuclear magnetic resonance spectrum of heterogeneous mixture of atorvastatin calcium.

Figure 4:

The solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form V atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION - Form V Atorvastatin

Form V atorvastatin was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form V atorvastatin was

measured germanium monochromated Cu K alpha 1(L =1.54056 Angstroms)

Equipment

STOE/STADI-P powder diffractometer with an IBM-PC compatible interface , STOE software = DIFFRAC AT (SOCABIM 1986, 1992). CuKa radiation (20 mA, 40 kV, k = 1.5406 A) slits I and II at 10) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 10 and IV at 0.150).

Methodology

The silicon standard is run each day to check the X-ray tube alignment. X-ray generator; sealed tube; 30KV; 5mA Curved PSD detector in the transmission mode, step size 0.03 degrees 2theta range 3-60 in two frames of 5 minutes exposure each per frame. Raw sample mounted on the transmission block on mylar (x-ray proof) film and rotated to avoid orientation effects. Table 1 lists the 2θ, d-spacings, and relative intensities of all lines in the ungrounded sample with a relative intensity for crystalline Form V atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity for Form V Atorvastatin

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9

8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5
26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7
30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

High resolution 13C spectra were obtained using high power proton decoupling and cross polarization with magic angle spinning at approximately 5 (8)kHz. The magic angle was adjusted using the 79Br signal of KBr by detecting the side bands as described by Frye et. Al. (J. Mag. Res., 1992, 48, 125). Approximately 150-200mg of the sample was packed into a canistor design rotor was used for each experiment. Chemical shifts was referred op the methine carbon of an external sample of admantane taken as 37.8 ppm with reference to tetrakis trimethylsilyl silane. Table 2 shows the solid-state NMR spectrum for crystalline Form V atorvastatin.

TABLE 2. Carbon Atom Assignment and Chemical Shift for Form V

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5

	122.7 120.1 117.0 112.9
C8, C10	72.3 69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

Crystalline Form V atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention.

The present invention also provides a process for the preparation of crystalline Form V atorvastatin which comprises exposing atorvastatin to a high relative humidity under conditions which yield crystalline Form V atorvastatin.

The precise conditions under which Form V of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method, which has been found to be suitable in practice.

Crystalline Form V atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an

aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending heterogeneous mixture of atorvastatin in water.

In general, the use of a hydroxylic co-solvent such as, for example, a lower alcohol, for example methanol and the like, is preferred. The following non-limiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt

(Form V Atorvastatin)

A heterogeneous mixture of Atorvastatin Calcium (10 g) stirred in a mixture of water and absolute ethanol (140 ml: 30 ml respectively) at 40 deg centigrade for 17 hrs. The product is filtered and sucked dried. The filtered semi dried product is dried in a vacuum tray drier (650 mm Hg) for 17 hrs to get 9 g of finished product.

X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrates the novel crystalline nature of the product - Form V as against the heterogeneous nature of the starting material (Figure 1 as shown in the accompanied drawings)

Solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium (Figure 4 as shown in the accompanied drawings) was compared with that of the heterogeneous mixture of form (Figure 3 as shown in the accompanied drawings) to confirm the observations.

Example 2

Indexing of Form V Atorvastatin Calcium

The indexing of the powder diffraction pattern of the Form V atorvastatin calcium was carried using THEOR90; in the suite of CRYSFIRE, a package for indexing powder x-ray diffraction pattern yielded the following results -

Total number of lines = 24
a = 11.338(3) A^o; $\alpha = 83.07(7)^o$
b = 11.058(4) A^o; $\beta = 73.47(11)^o$
c = 17.249(11) A^o; $\gamma = 68.12(4)^o$
V = 1923.83 A^{o3}

We claim:

1. Crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ, d-spacings, and relative intensities measured using CuK radiation:

2θ-OBS	2θ-CALC	D-OBS	Relative Intensity(%)
5.340	5.340	16.5350	7.9
8.618	8.611	10.2525	23.1
8.724	8.697	10.1282	25.2
8.950	8.946	9.8727	30.1
9.819	9.828	9.0004	28.7
10.094	10.063	8.7564	20.0
11.335	11.337	7.8004	21.0
16.673	16.671	5.3128	100.0
17.955	17.947	4.9363	19.3
19.161	19.132	4.6283	43.3
21.479	21.479	4.1338	69.2
22.561	22.568	3.9378	38.3
23.154	23.122	3.8384	43.2
23.576	23.588	3.7707	33.7
24.324	24.309	3.6563	6.6
24.560	24.559	3.6217	10.5
26.268	26.295	3.3900	8.1
28.224	28.217	3.1593	9.8
28.804	28.781	3.0970	9.9
29.199	29.195	3.0560	21.7

30.370	30.371	2.9408	10.8
31.893	31.909	2.8037	12.3
37.356	37.337	2.4053	10.3

2. Crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment Chemical Shift

Assignment (8kHz)	Chemical Shift
Spinning Side Band	59.64
Spinning Side Band	157.9
Spinning Side Band	161.59
C12 or C25	183.4
C12 or C25	177.6
C16	166.4 159.5
Aromatic Carbons C2-5, C13-C18, C19-24, C27-C32	136.4 134.4 130.2 128.8 127.5 122.7 120.1 117.0 112.9
C8, C10	72.3

	69.5 67.3 64.0
Methylene Carbons C6, C7, C9, C11	46.5 40.5
C33	25.5 24.0
C34	20.42

3. A process for the preparation of Form V crystalline atorvastatin Calcium and hydrates thereof which comprises

(iv) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;

(v) filtering to get the solid;

(vi) drying to get Form V atorvastatin calcium.

4. A process of claim 3 wherein the ratio of water and absolute ethanol is in the range of 3:1 to 8 :1.

5. A process of claim 4, wherein the ratio of water and alcohol is 4.67: 1.

6. A process of claim 3, wherein the stirring is carried out at 25 - 50 deg centigrade.

7. A process of claim 6, wherein the stirring is carried out at 40 deg centigrade.

8. A process of claim 3, wherein the stirring is carried out for 10 - 25 hrs.

9. A process of claim 8, wherein the stirring is carried out for 17 hours.

10. A process of claim 3, wherein the final product is dried in vacuum tray drier.

Figure 1

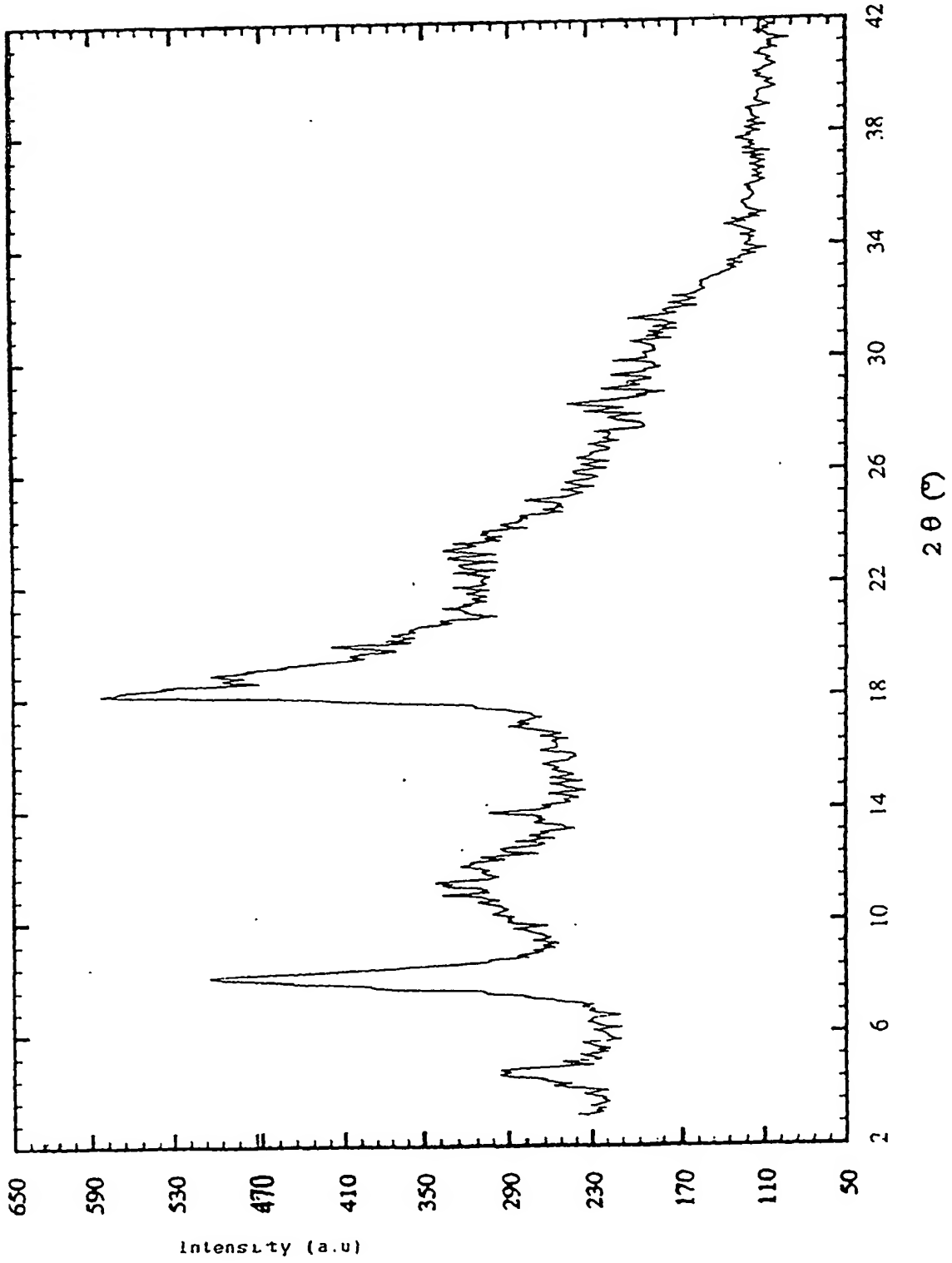

650
590
530
470
410
350
290
230
170
110
50
Intensity (a.u)
2
6
10
14
18
22
26
30
34
38
42
2 θ (°)

Figure 2

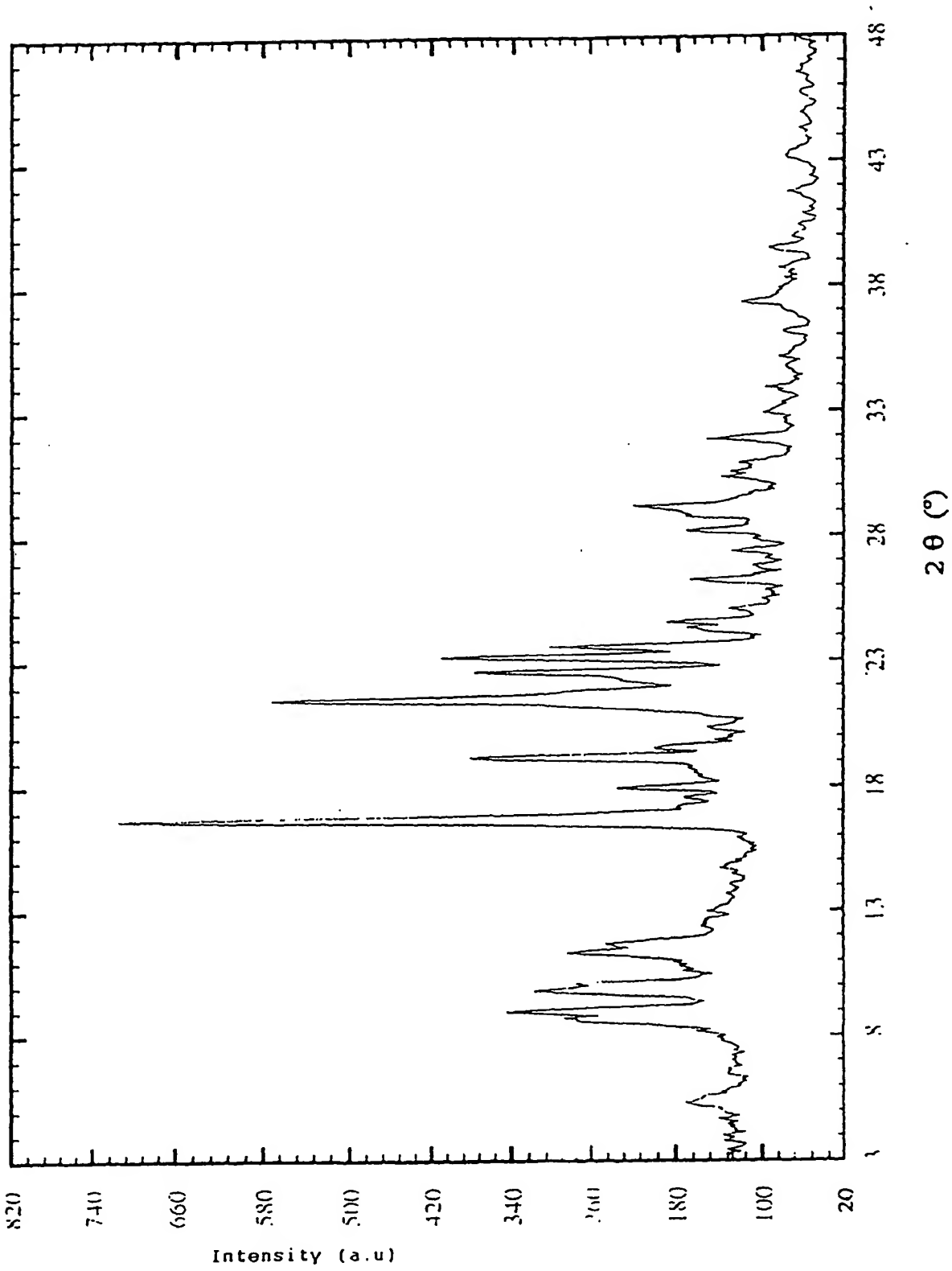

Intensity (a.u)
820
740
660
580
500
420
340
260
180
100
20
3
8
13
18
23
28
33
38
43
48
2 θ (°)

Figure 3

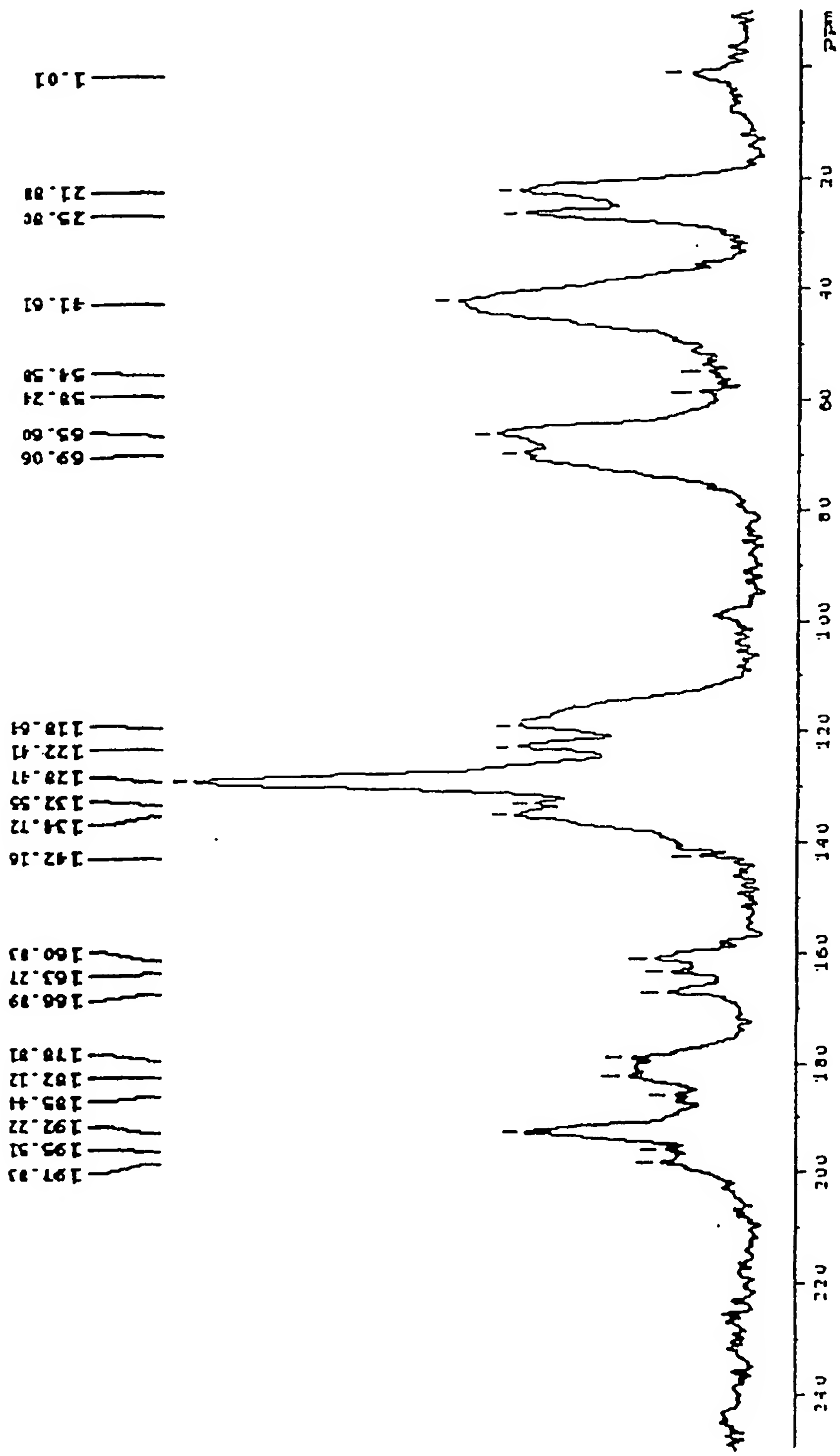
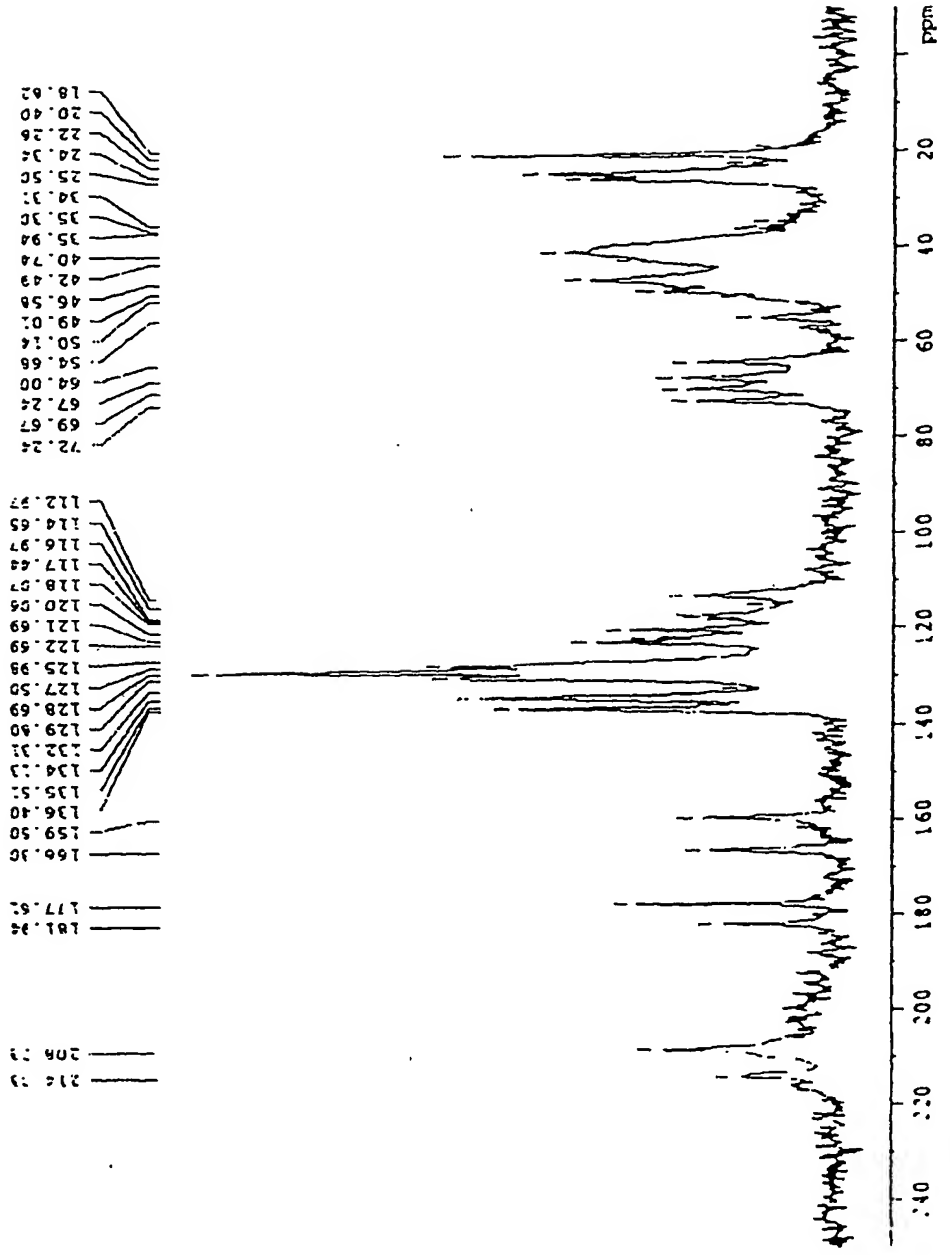


Figure 4



INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/IN 01/00006

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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E	WO 01 36384 A (TEVA PHARMA ;AYALON ARI (IL); NIDDAM VALERIE (IL); ROYTBLAT SOFIA) 25 May 2001 (2001-05-25) the whole document	1-10
A	WO 97 03958 A (WARNER LAMBERT CO ;MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2001	20/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Von Daacke, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 98 04543 A (WARNER LAMBERT CO ;BUTLER DONALD EUGENE (US); JACKS THOMAS ELLIOTT) 5 February 1998 (1998-02-05) example 8	2
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